VITREOUS CAVITY PENETRATION OF CEFTAZIDIME AFTER INTRAVENOUS ADMINISTRATION

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Purpose: Penetration of ceftazidime, a third generation cephalosporin, into the vitreous cavity after intravenous administration was investigated.

Methods: Because antimicrobial penetration varies with surgical status of the eye and with inflammation, studies were conducted in phakic, aphakic, and aphakic, vitrectomized eyes in both normal and inflamed conditions. Ceftazidime 50 mg/kg was administered every 8 hours and vitreous cavity concentrations were tested at intervals from 2 to 72 hours after the initial dose.

Results: No penetration was found into control phakic and aphakic eyes, but drug concentrations were detected in inflamed eyes at 24 hours. Vitreous concentrations of ceftazidime in aphakic, vitrectomized eyes reached levels well above the minimal inhibitory concentration (MIC) for Pseudomonas organisms within 2 hours of intravenous administration in control eyes (8.5 μg/ml) and inflamed eyes (35.4 μg/ml). Inflammation and removal of the lens and vitreous significantly enhanced ceftazidime penetration at all time periods tested.

Conclusion: Ceftazidime penetrates into the vitreous cavity of inflamed eyes after intravenous administration and achieves concentrations above the MIC for Pseudomonas organisms. Penetration is greatest in aphakic, vitrectomized eyes.

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Ceftazidime is a potent, third-generation, semi-synthetic cephalosporin with promise for use in the treatment of gram-negative endophthalmitis.[1–3] Vancomycin is well established as the drug of choice for treatment of gram-positive endophthalmitis because staphylococcal organisms, *Streptococcus, P. acnes,* and *Bacillus* are almost uniformly susceptible.[4,5] Vancomycin, however, has essentially no gram negative coverage, and an agent for initial intravenous use against gram-negative organisms is needed. Aminoglycosides have significant limitations because of their poor penetration into the vitreous cavity after intravenous administration,[6–8] and when combined with vancomycin the nephrotoxic and ototoxic complications of the two agents may be additive.

Studies of gram-negative endophthalmitis by Irvine[9] and Donahue[10] demonstrated that almost all organisms producing gram-negative endophthalmitis were susceptible to ceftazidime. Ceftazidime was chosen by the Endophthalmitis Vitrectomy Study Group to be administered intravenously along with amikacin in those patients randomized to receive intravenous antibiotic therapy.[11] The spectrum of activity is particularly good for *Pseudomonas,* with ceftazidime being the best of the third-generation cephalosporins for treatment of *Pseudomonas* infections. Ceftazidime is the least active drug of the third-generation cephalo-

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Table 1. Intraocular Penetration of Ceftazidime after Intravenous Administration, Experimental Design, and Vitreous Samples Obtained at Each Time Period

	Phakic Eyes (Group 1)		Aphakic Eyes (Group 2)		Aphakic/Vitrectomized Eyes (Group 3)	
Hours after injection	Control	Inflamed	Control	Inflamed	Control	Inflamed
2	4	3	4	4	4	8
8	4	4	4	4	—	8
10	—	—	—	—	4	4
24	4	4	4	4	4	8
26	—	—	—	—	4	4
48	4	4	4	4	4	8
72	—	—	—	—	4	5

sporins against gram-positive organisms, however, with limited activity against both *Staphylococcus epidermidis* and *S. aureus*.[1]

The third-generation cephalosporin agents must be given parenterally. Many have good penetration into the cerebrospinal fluid and achieve sufficient levels to treat bacterial meningitis, a major advance over first- and second-generation agents.[1,12-14] Ceftazidime has good penetration into cerebrospinal fluid, partially related to relatively low protein binding,[15] and has been found useful in the treatment of meningitis, suggesting a possible advantage in ocular penetration. Cerebrospinal fluid concentrations of 40 μg/ml have been reported to be achieved.

Because of these promising characteristics, we evaluated penetration of ceftazidime into the rabbit eye after intravenous administration. Because the surgical status of the eye influences penetration of antibiotics into the vitreous cavity, we studied penetration into phakic, aphakic, and aphakic, vitrectomized eyes. Because inflammation may break down the blood–ocular barrier, both control and inflamed eyes were evaluated.

Material and Methods

We divided 46 New Zealand albino rabbits (87 eyes) into 4 experimental groups. The experimental protocol was to study the ocular pharmacokinetics of ceftazidime in three anatomic conditions (phakic, aphakic, and aphakic, vitrectomized eyes). Penetration of ceftazidime into the vitreous cavity after intravenous administration was studied in phakic (group 1), aphakic (group 2), and aphakic, vitrectomized (group 3) eyes (Table 1). Cefazolin levels after intraocular injection supplemented by intravenous injection were studied in a final group (group 4). Each anatomic group was then subdivided into control and inflamed subgroups. All animals were maintained in accordance with the guidelines of the Association for Research in Vision and Ophthalmology.

For all surgical procedures the animals were anesthetized by intramuscular injections of a 50/50 mixture of xylazine hydrochloride (10 mg/kg) and ketamine hydrochloride (30 mg/kg). Retrobulbar injections of 1 cc lidocaine hydrochloride 2% were performed in each group for extended surgical manipulation. Eyes were dilated with phenylephrine 2.5% and mydriacyl 1%.

For lensectomy, a limbal incision was created and a capsulorhexis was performed. Phacoemulsification was performed by introduction of an irrigating/aspiration handpiece into the limbal incision, and removal of the lens was accomplished with fragmentation and irrigation of balanced salt solution with addition of heparin 2500 units/500 cc. The posterior capsule was opened with a bent needle. The limbal incision was closed with multiple interrupted #9-0 monofilament sutures. At the close of the procedure gentamicin 12 μg and dexamethasone 1.2 mg were injected subconjunctivally. The eyes were allowed to heal for 3 weeks and were periodically evaluated for resolution of inflammation.

In eyes prepared for the aphakic, vitrectomized group, the lensectomy was carried out and the incision then closed. An infusion cannula was then introduced through the pars plana 2 mm posterior to the limbus and incisions were made at the same distance from the limbus for insertion of the vitrectomy instrument. A core vitrectomy was performed without attempts to remove the cortical vitreous. Incisions were closed with a #7-0 Vicryl suture. Periocular injections and postoperative monitoring of these eyes was the same as for eyes undergoing lensectomy alone.

Inflammation was produced in one eye of each animal using injection of heat-killed *S. epidermidis*, as in the model described by Martin et al.[16] In almost all

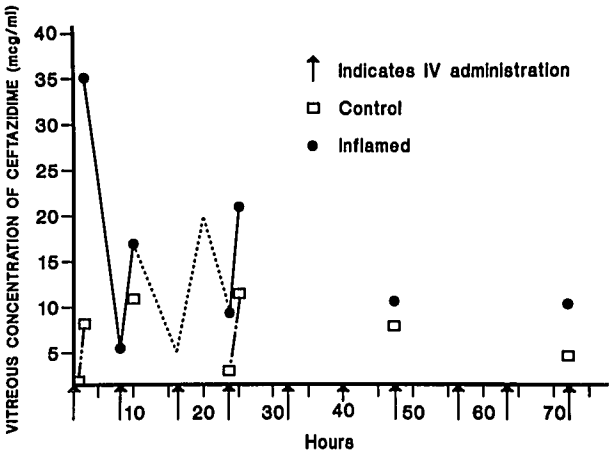

Fig. 1. Peak and trough concentrations of ceftazidime. Intravenous administration is indicated by arrows, and dotted lines are estimated values.

cases the fellow eye was maintained as a control. The number of injected organisms was 10^9/0.1 ml in phakic eyes; 10^7/0.1 ml in aphakic eyes; and 10^7/0.1 ml in aphakic, vitrectomized eyes. Eyes were observed for 24 hours after injection of the heat-killed *S. epidermidis* and reexamined to ensure equivalent degrees of inflammation. Antibiotic administration began 24 hours after injection of the organisms.

Ceftazidime 50 mg/kg was injected intravenously into rabbits at time zero and every 8 hours thereafter for the duration of the experiment. Blood samples were obtained 15, 30, 45, and 60 minutes and at 7.5, 23.5, and 47.5 hours after injection.

In the phakic (group 1) and aphakic (group 2) groups, animals were killed at 2, 8, 24, and 48 hours after time zero by intravenous injection of xylazine and ketamine. The number of eyes for each sampling period for each subgroup is given in Table 1. The eyes were enucleated and the vitreous harvested by rapid freezing of the globe in liquid nitrogen, followed by dissection to isolate the vitreous. In each subgroup at least four eyes were sampled, except for one group in which one animal died.

In the aphakic, vitrectomized group (group 3) animals were anesthetized at 2, 8, 10, 24, 26, 48, and 72 hours and 0.15 ml removed from the vitreous cavity for analysis as described above. One set of eyes was sampled at 2, 8, 24, 48, and 72 hours. Another set was sampled at 10 and 26 hours to reduce the artifact of repeated sampling from the same eyes. This produced data from time periods just before intravenous injection (8, 24, 48, and 72 hours) and 2 hours after injection (2, 10, and 26 hours).

In two animals 2.25 mg ceftazidime was injected into the vitreous cavity and 50 mg/kg ceftazidime injected intravenously followed by repeat intravenous injections every 8 hours for 48 hours (group 4). After 48 hours samples were removed from the vitreous cavity as described above.

Ceftazidime concentrations in vitreous fluid were determined by a modification of an agar well diffusion assay by using a clinical isolate of *Escherichia coli* as the test organism. The assay medium was antibiotic medium (Difco Laboratories, Detroit, MI) to which paraaminobenzoic acid (Sigma, St. Louis, MO) and thymidine (Sigma) were added. Standards and controls were prepared by dissolving ceftazidime (Eli Lilly Pharmaceutical Co., Indianapolis, IN) in sterile 0.1 sodium phosphate buffer (pH 7) and diluting the solutions in heat-inactivated pooled normal human serum for standards with concentrations of 12.5, 25, 50, and 100 μ/ml. For assay, 25 ml of each sample was placed in precut seeded agar wells. After inoculation of the wells with standards, controls, and samples, the microbiologic plates were allowed to prediffuse at 4°C for 1 hour before incubation at 35°C for 16 to 24 hours. Inhibition zone diameters were measured, and the serum concentration was calculated from the appropriate standard curves.

Results

The serum level 15 minutes after intravenous injection was 117 μg/ml. In both the phakic (group 1) and aphakic (group 2) control eyes no ceftazidime was identified in the eyes at any time period after intravenous administration was begun (Table 2). No detectable concentrations of drug were identified in the inflamed eyes until 24 hours after the drug was begun in the phakic (11.3 ± 8.01 μg/ml) and aphakic (1.4 ± 2.7 μg/ml) inflamed eyes. At 48 hours, concentrations were slightly decreased in phakic eyes (4.6 ± 1.58 μg/ml) and somewhat increased in aphakic eyes (5.1 ± 1.74 μg/ml).

Values in inflamed aphakic, vitrectomized eyes (group 3) after intravenous injection were: 2 hours, 35.4 ± 6.25 μg/ml; 10 hours, 17 ± 3.29 μg/ml; and 26 hours, 21.2 ± 2.06 μg/ml. Values immediately before intravenous injection were: 8 hours, 5.4 ± 2.06 μg/ml; 24 hours, 9.28 ± 2.22 μg/ml; 48 hours, 10.65 ± 2.45 μg/ml; and 72 hours, 10.16 ± 2.66 μg/ml. This produced a saw-toothed pattern of concentration when data points were estimated for times not tested (Figure 1). Aphakic, vitrectomized control eyes demonstrated significant concentrations of drug at the time periods 2 hours after intravenous dosing (2 hours, 8.4 ± 0.74 μg/ml; 10 hours, 12.5 ± 5.42 μg/ml; 26 hours, 12.0 ± 2.27 μg/ml). Lower concentrations were identified immediately before intravenous injection (24 hours,

Table 2. Measured Intraocular Ceftazidime Concentrations after Intravenous Injection

	Phakic Eyes (Group 1)		Aphakic Eyes (Group 2)		Aphakic/Vitrectomized Eyes (Group 3)	
Hours after injection	Control	Inflamed	Control	Inflamed	Control	Inflamed
2	0	0	0	0	8.4 ± 0.74	35.4 ± 6.25
8	0	0	0	0	—	5.4 ± 2.06
10	—	—	—	—	12.5 ± 5.42	17.0. ± 3.29
24	0	11.3± 8.01	0	1.4 ± 2.7	2.05 ± 2.05	9.28 ± 2.22
26	—	—	—	—	12.0 ± 2.27	21.25 ± 2.06
48	0	4.6 ± 1.58	0	5.1 ± 1.74	8.3 ± 0.86	10.65 ± 2.45
72	—	—	—	—	4.85 ± 2.85	10.16 ± 2.66

Concentrations of ceftazidime are given in mcg/ml, ± standard error of the mean.

2.05 ± 2.05 μg/ml; 48 hours, 8.3 ± 0.86 μg/ml; and 72 hours, 4.85 ± 2.85 μg/ml).

In the eyes given intraocular injections and also given intravenous ceftazidime every 8 hours beginning at time zero, the values at 48 hours were 6.9 μg/ml for control eyes and 8.0 μg/ml for inflamed eyes.

Calculating penetration ratios as the average concentration of intraocular antibiotic (maximum value) divided by the serum concentration determined 15 minutes after intravenous administration yielded the following values: phakic inflamed 10.0%; aphakic inflamed 4.5%; aphakic, vitrectomized control 10.9%; aphakic, vitrectomized inflamed 39%.

Discussion

These studies suggest that intravenous ceftazidime may play an important role in the prophylaxis and treatment of endophthalmitis. Significant penetration of ceftazidime into the inflamed aphakic, vitrectomized eye was found 2 hours after a single bolus intravenous dose. The average concentration at this time was 35.4 μg/ml, with a penetration ratio of 39% of the peak plasma levels. These values might have been higher if tested 1 hour after the bolus dose, although aqueous concentration peaks 1 hour after intravenous administration and remains stable for between 1 and 3 hours after the bolus dose.[17]

The penetration ratio is higher than the 21.5% penetration ratio reported for cerebrospinal fluid in humans with inflamed meninges[2]; concentration levels at 10 and 26 hours are lower and the penetration ratios are more comparable to cerebrospinal fluid penetration ratios (15% and 18%, respectively). The vitreous concentration value is significantly higher than the 7.3 μg/ml concentration reported for non-inflamed aqueous levels in the rabbit, but is less than the penetration ratio of 64% and concentration of 54 μg/ml in aqueous from the inflamed rabbit eyes.[18] This concentration of ceftazidime achieved in inflamed aphakic, vitrectomized eyes is therapeutically significant; it is 9 times the average minimum inhibitory concentration (MIC) for *P. aeruginosa* and more than 30 times the MIC for *Streptococcus, Klebsiella, Serratia, E. coli,* and *H. influenzae.*[2]

Although a single intravenous dose of ceftazidime can achieve intravitreal concentrations that should be sufficient for bacterial killing in the inflamed, aphakic, vitrectomized eye, gentamicin administered intravenously has not been shown to reach intraocular therapeutic concentrations in human or animal studies with the vitreous intact.[6-8]

Although bacterial killing studies have not been done for ceftazidime in the treatment of endophthalmitis, beta-lactam antibiotics in general need prolonged levels above the MIC for effective action. Injection of ceftazidime 2.25 mg into the monkey vitreous cavity did not produce toxic changes[3] and appears to be a safe intravitreal dose for humans, although clinical experience is limited. A dose of 2 mg may be chosen to make the dilution procedure easier. The half-life of ceftazidime is 8.7 hours after intravitreal injection into the inflamed aphakic eye and 5.1 hours after injection into the inflamed aphakic, vitrectomized eye of the rabbit.[19] Potentially effective concentrations of the drug are maintained for approximately 60 hours in the aphakic inflamed eyes and for less than 48 hours in the aphakic, vitrectomized, inflamed eye. Supplementation by intravenous administration may be indicated, especially after vitrectomy when the half-life of the drug is short. The usual doses are 1 to 2 g every 8 hours in adults; the higher dose will produce a higher serum level, which in turn favors movement across the blood–ocular barriers.

. The pattern of peak and trough demonstrated in the vitreous after intravenous injection gives a saw-tooth appearance to graphed values from the inflamed eye

consistent with an increased penetration across the blood–ocular barriers and short half-life with rapid elimination from the vitreous cavity. This pattern of penetration into the vitreous cavity is different from that of cefazolin. Cefazolin concentrations demonstrate a slow buildup with increasingly higher levels over 49 hours of testing, although only the peak and not the trough levels were evaluated. For cefazolin, the concentration at 49 hours was 3 times as high as the concentration 1 hour after the initial injection.[16] The penetration ratio after the initial dose was, therefore, 4%, rising to 15.4% after 49 hours, demonstrating that the inflamed rabbit eye is considerably more permeable to ceftazidime than to cefazolin.

In the aphakic, vitrectomized control eyes there was an apparent similar saw-tooth pattern to concentrations, although the range of values from trough to peak was smaller, indicating less permeability than in inflamed eyes. The findings were consistent with the increase in concentration secondary to inflammation noted in aqueous humor levels, where concentrations were almost eight times higher in inflamed eyes than in control eyes.[18] The vitreous cavity concentrations achieved in the control eyes were above the MIC for *Pseudomonas,* but only by a factor of 1, whereas they were 8 times the MIC for other significant gram-negative organisms.

The effects of the inflammation were also noted in phakic and aphakic eyes without vitrectomy. There was no penetration into eyes without inflammation, which is consistent with the findings of Walstad.[20] Even with inflammation, significant concentrations of drug did not appear in the vitreous until 24 hours after the first intravenous bolus dose. In the phakic eye the levels exceeded the MIC for *Pseudomonas* by a factor of 3, and other gram-negative organisms by a factor of 10 at the 24-hour sampling time. Forty-eight hours after the beginning of the drug administration, the concentrations were essentially equivalent in aphakic and phakic eyes, with levels of 5.1 μg/ml and 4.6 μg/ml, respectively.

There was drug penetration into the vitrectomized control eyes but not into the phakic or aphakic control eyes, further underscoring the idea that the vitreous is a barrier to permeability. Significant concentrations after intravenous administration have been identified in the aqueous humor,[17,20] indicating that intravenous administration may play a potential role in the treatment of bleb infections or prophylactic treatment of anterior segment wounds.

When intravenous administration is begun after an intraocular injection, it is unlikely that there is significant penetration into the vitreous cavity from plasma during the initial phases of intraocular drug clearance. During most of the early phase of the intraocular elimination, the intraocular concentration is higher than the plasma concentration, so no concentration gradient is present. Therefore, unless active transport from plasma is involved, there is not a direct contribution from plasma to the intraocular concentration. For phakic and aphakic inflamed eyes vitreous levels remain above peak plasma levels until 18 to 36 hours after intravitreal injection, and they remain at this level for 10 to 12 hours in aphakic, vitrectomized eyes.

The intravenous dose may prolong the time during which concentrations stay at or above 35 μg/ml in inflamed, aphakic, vitrectomized eyes. The relatively high plasma concentration establishes a gradient favoring penetration into the eye as the intravitreal concentration falls. Without active transport from the eye, however, the concentration gradient will not favor clearance from the eye and should prolong high levels. This effect on concentrations is short lived, and the concentrations 48 hours after intraocular administration supplemented by intravenous administration were the same as those identified after intravitreal administration only. Thus, the main potential advantage for intravenous administration of ceftazidime is the concentrations it achieves through penetration into the vitreous cavity, rather than alterations in the clearance of the drug injected directly into the vitreous cavity.

The dosage of ceftazidime for adult infections is 1 g intravenously or intramuscularly every 8 hours, but in serious infections 2 g may be administered.[21] The pediatric dosage is 50 mg/kg every 8 hours.

Key words: ceftazidime, vitreous, antibiotic, gram-negative endophthalmitis.

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